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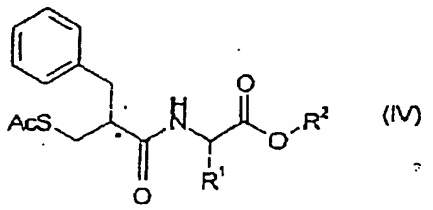
(54) Method for producing an optically active phenylpropionic acid derivative

(57) Optically active N-[(S)-2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine esters derivatives of formula (IV)(wherein R^1 represents hydrogen, an optionally substituted amino acid side chain or a protected amino acid chain; R^2 represents and optionally substituted linear of branched C_1 to C_{18} alkyl group, or an optionally substituted benzyl group; and * denotes an optionally active carbon atom) useful as enkephalin inhibitory agents of ACE inhibitory agents can be produced at low cost in an industrial manner, by subjecting optically active 2-hydroxymethyl-3-phenylpropionic acid and glycine esters to condensation, subsequently converting the hydroxyl group into an elimination group, and substituting the elimination group with an acetylthio group.



(IV)

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Description

[0001] The present invention relates to a method for producing an optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester. The present invention is useful for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester.

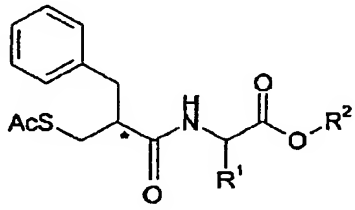
[0002] (S)-N-[2-(Acetylthiomethyl)-1-oxo-3-phenylpropyl]glycine benzyl ester which has an inhibitory action against angiotensin converting enzyme is useful as a therapeutic agent for treatment of deteriorated cardiovascular systems, hypertension, cardiac function impairment and liver function impairment.

Alternatively, the (R) form thereof which has an inhibitory action on enkephalinase is useful as an analgesic, antidiarrheic, and antacid (JP-A-2-161 and JP-A-8-59606). Known methods for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester include a method comprising optically resolving racemic 2-acetylthiomethyl-3-phenylpropionic acid by using ephedrine and subjecting one of the resulting products to condensation with glycine benzyl ester and N, N'-dicyclohexylcarbodiimide (JP-A-8-59606). According to that method, however, the efficiency of the optical resolution of 2-acetylthiomethyl-3-phenylpropionic acid with ephedrine is so low that the method is not practical. Furthermore, the method is so problematic in terms of the generation of such an enormous volume of sulfur-containing wastes that the method cannot be said to be industrially advantageous.

[0003] It is an object of the present invention to provide a method for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester, particularly optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester, in an inexpensive manner which is suitable for industrial production.

[0004] The inventors have found a method for producing N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester, comprising subjecting optically active 2-hydroxymethyl-3-phenylpropionic acid and an amino acid ester to condensation, converting the hydroxyl group into an elimination group, and substituting the elimination group with an acetylthio group.

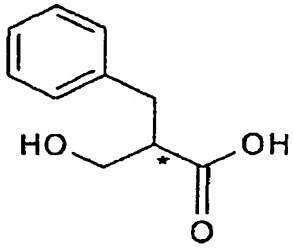
[0005] More specifically, the invention relates to a method for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester represented by the general formula (IV);



(IV)

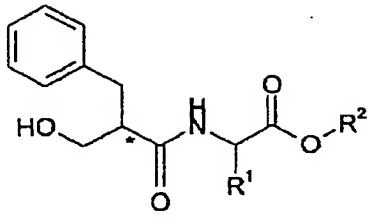
(wherein R_1 represents hydrogen, an amino acid side chain or a protected amino acid side chain; R_2 represents an optionally substituted linear or branched C_1 to C_{18} alkyl group, or an optionally substituted benzyl group; and * denotes an optically active carbon atom),

comprising subjecting optically active 2-hydroxymethyl-3-phenylpropionic acid represented by the general formula (I);



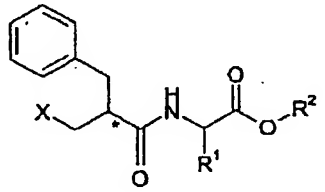
(I)

(wherein * denotes an optically active carbon atom) to reaction with an amino acid ester or a salt thereof to convert it into optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-amino acid ester represented by the general formula (II);



(II)

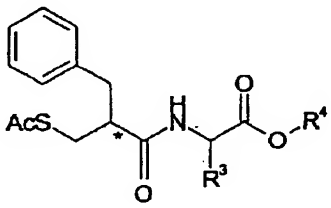
(wherein R_1 and R_2 independently represent the same groups as described above; * denotes an optically active carbon atom),
activating the hydroxyl group of the hydroxymethyl group at the 2-position to convert the compound of formula (II) into an optically active N-acylamino acid ester represented by the general formula (III);



(III)

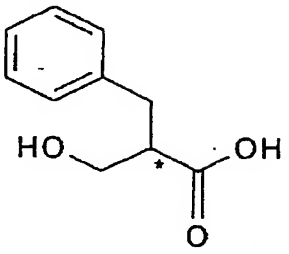
(wherein R_1 and R_2 independently represent the same groups as described above; X represents chloride, bromide, iodide, a linear, branched or cyclic C_1 - C_6 alkylsulfonyloxy group which may or may not have a substituent, or a C_6 - C_{18} arylsulfonyloxy group; and * denotes an optically active carbon atom),
and further subjecting the resulting optically active N-acylamino acid ester to reaction with thioacetic acid in the presence of a thioacetate salt or a base.

[0006] The present invention is particularly useful for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester. More specifically, the invention relates to a method for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester represented by the general formula (V);



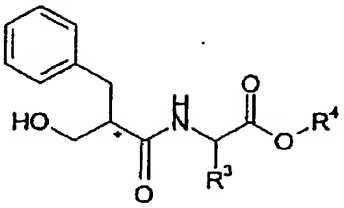
(V)

(wherein R_3 represents hydrogen; R_4 represents a benzyl group; and * denotes an optically active carbon atom), comprising subjecting optically active 2-hydroxymethyl-3-phenylpropionic acid represented by the general formula (I);



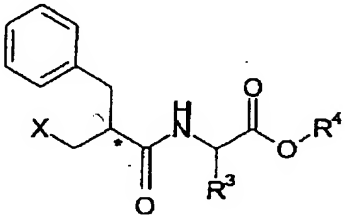
(I)

(wherein * denotes an optically active carbon atom) to reaction with glycine benzyl ester or a salt thereof to convert it into optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester represented by the general formula (VI);



(VI)

(wherein R_3 represents hydrogen; R_4 represents benzyl group; and * denotes an optically active carbon atom), activating the hydroxymethyl group at the 2-position by conversion of the compound of formula VI into an optically active N-acylglycine benzyl ester represented by the general formula (VII);



(VII)

(wherein X represents chloride, bromide, iodide, a linear, branched or cyclic C_1 - C_6 alkylsulfonyloxy group which may or may not have a substituent, or a C_6 - C_{18} arylsulfonyloxy group; R_3 represents hydrogen; R_4 represents a benzyl group; and * denotes an optically active carbon atom),
and further subjecting the resulting N-acylglycine benzyl ester to reaction with thioacetic acid in the presence of a thioacetate salt or a base.

[0007] Additionally, significant intermediates according to the method, namely the optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester represented by the general formula (VI) and the optically active N-acylglycine benzyl ester represented by the general formula (VII) are also encompassed within the scope of the present invention.

[0008] The optically active 2-hydroxymethyl-3-phenylpropionic acid (I) for use as a raw material in accordance with the invention, can be prepared by optically resolving racemic 2-hydroxymethyl-3-phenylpropionic acid by using an optically active amine such as (1R,2S)-(+)-cis-1-amino-2-indanol (JP97-270680).

[0009] The amino acid in the amino acid ester or salt thereof for use as the raw material in accordance with the invention includes glycine, phenylglycine, alanine, glutamine, asparagine, valine, leucine, isoleucine, proline, methionine, serine, threonine, phenylalanine, naphthylalanine, tyrosine, 3,4-dihydroxyphenylalanine tryptophan, histidine, glutamic acid, aspartic acid, lysine, and arginine. These amino acids may, optionally, have substituents at the side chains thereof. Examples of substituent include C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups, halogen atoms and nitro

groups. Furthermore, any reactive functional group within the side chains is preferably protected with a protective group suitable for use in peptide synthesis, for example an ester-type protective group such as a methyl ester, ethyl ester, or benzyl ester for carboxyl groups; an acyl group such as a formyl group, acetyl group, trifluoroacetyl group, benzoyl group, t-butyloxycarbonyl group or benzyloxycarbonyl group for amino groups; and an ether-type protective group such as a benzyl ether or t-butyl ether or an ester-type protective group such as acetyl or benzoyl for hydroxyl groups.

[0010] In the amino acid ester, the α-carboxyl group has been esterified as a preliminary. Examples of the ester include methyl ester, ethyl ester and benzyl ester. The ester may, optionally, have substituents. Examples of substituent include C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups, halogen atoms and nitro groups. Because the α-carboxyl group of the amino acid in one embodiment of the final compound, namely N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester is a benzyl ester, the amino acid ester is preferably in the form of benzyl ester. The amino acid ester in the objective compounds may satisfactorily be deprotected in a conventional manner.

[0011] The reaction of optically active 2-hydroxymethyl-3-phenylpropionic acid (I) with an amino acid ester to convert the phenylpropionic acid (I) into optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-amino acid ester (II) is promoted by use of a condensation process for use in general peptide synthesis.

[0012] More specifically, optically active 2-hydroxymethyl-3-phenylpropionic acid (I) is subjected to reaction with an amino acid ester in the presence of a condensation agent in a solvent.

[0013] Suitable condensation agents for use in the reaction include N, N'-dicyclohexylcarbodiimide, a water-soluble carbodiimide, carbonyldiimidazole, and diphenylphosphoryl azide. Glycine benzyl ester or other amino acid ester may be used in the free form or in the form of a salt with hydrochloric acid, sulfuric acid, p-toluenesulfonic acid, methanesulfonic acid and the like. Use may be made of solvents such as hydrocarbon halides such as dichloromethane and chloroform; ethers such as tetrahydrofuran and methyl tert-butyl ether; acetate esters such as ethyl acetate and isopropyl acetate; nitriles such as acetonitrile; aromatic hydrocarbons such as toluene and xylene; dimethylformamide and dimethylsulfoxide.

[0014] Additionally, bases such as triethylamine, pyridine, N-methylmorpholine, and 4-dimethylaminopyridine may optionally be present concurrently in the reaction system. Still further, additives such as N-hydroxysuccinimide and 1-hydroxybenzotriazole may also be used.

[0015] The conversion of optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-amino acid ester (II) into optically active N-acylamino acid ester (III) by activating the hydroxyl group of the hydroxymethyl group at the 2-position of the amino acid ester (II) can be promoted by alkylsulfonation, arylsulfonation or halogenation or the like for general use in the activation of hydroxyl group.

[0016] The hydroxyl group may be alkylsulfonated or arylsulfonated by the action of a sulfonation agent in the presence of a base. Examples of the sulfonation agent include methanesulfonyl chloride, p-toluenesulfonyl chloride, benzenesulfonyl chloride, p-nitrobenzenesulfonyl chloride, and trifluoromethanesulfonyl chloride. Examples of the base include triethylamine, pyridine, 4-dimethylaminopyridine, and N-methylmorpholine.

[0017] The hydroxyl group may be halogenated via the action of halogenating agents such as thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, and phosphorus tribromide or via the action of halogenating agents, in the presence of triphenylphosphine, such as N-chlorosuccinimide, N-bromosuccinimide, bromide, carbon tetrachloride and carbon tetrabromide. Alternatively, the halogenation of the hydroxyl group comprises alkylsulfonating, arylsulfonating or haloformylating the hydroxyl group, and subsequently subjecting the resulting halogenated hydroxyl group to reaction with lithium chloride, lithium bromide, sodium bromide, potassium bromide, magnesium bromide, tetra-(n-butyl)ammonium bromide or sodium iodide.

[0018] The optically active 2-hydroxymethyl-3-phenylproplonic acid (I) can be converted into optically active N-acylamino acid ester (III) at one step, by subjecting the 2-hydroxymethyl-3-phenylpropionic acid (I) to reaction with thionyl chloride or thionyl bromide or the like to convert the carboxyl group into an acid chloride and concurrently preparing the hydroxyl group into an elimination group such as halogen or sulfinyloxychloride group and subjecting the elimination group to reaction with amino acid ester.

[0019] The optically active N-acyl-amino acid ester (III) can be converted into optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester (IV), by subjecting the optically active N-acylamino acid ester (III) to reaction with a thioacetate salt or reaction with thioacetic acid in the presence of a base. The thioacetate salt includes potassium thioacetate, sodium thioacetate, lithium thioacetate, and cesium thioacetate.

[0020] For the aforementioned reaction, any inorganic base or organic base may be used together with thioacetic acid; examples of inorganic base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, and cesium carbonate; and examples of organic base include triethylamine, pyridine, N-methylmorpholine, and diisopropylethylamine.

[0021] For the reaction, the thioacetic acid salt, thioacetic acid and base may suitably be used at 1.0 to 4.0 equivalents, preferably 1.0 to 2.0 equivalents. Suitable solvents includes hydrocarbon halides such as dichloromethane and chloroform; ethers such as tetrahydrofuran and methyl tert-butyl ether; ketones such as acetone and 4-methyl-2-pentanone; acetate esters such as ethyl acetate and isopropyl acetate; nitriles such as acetonitrile; aromatic hydrocarbons

such as toluene and xylene; and dimethylformamide and dimethylsulfoxide. The reaction temperature is suitably between 0 and 100 °C, preferably 20 to 60 °C.

[0022] The objective compound can be isolated, by removing impurities via procedures such as extraction after completion of the reaction and depositing the crystal in an appropriate solvent. Then, procedures for example column chromatography may also be conducted.

[0023] When amino acid side chains are protected, generally, deprotection is conducted finally by a general procedure. Thus, the objective compound can be obtained.

[0024] The present invention will now be described in more detail with reference to examples and reference examples, but the invention is not limited to these examples.

Reference Example 1

Synthesis of 3-hydroxy-2-methylene-3-phenylpropionate methyl ester:

[0025] A mixture of benzaldehyde (63.67 g; 600 mmol), methyl acrylate (60 ml; 667 mmol) and 1,4-diazabicyclo [2.2.2]octane (13.46 g; 120 mmol) was stirred at ambient temperature for 119 hours. To the reaction solution were added water (60 ml), 37 % hydrochloric acid (60 ml) and ethyl acetate(120 ml), and then, the organic phase was extracted. The resulting organic phase was washed twice with saturated saline (60 ml), dried over anhydrous sodium sulfate and filtered, followed by concentration under reduced pressure, to give a crude product of the title compound at a yield of 108.8 g. ^{1}H-NMR ($CDCl_3$) d: 3.12 (1H, s), 3.69 (3H, s), 5.55 (1H,s), 5.83 (1H,s), 6.33 (1H,s), 7.29-7.37 (5H, m).

Reference Example 2

Synthesis of 2-benzylidene-3-acetoxypropionate methyl ester:

[0026] The product (108.8 g) in Reference Example 1, namely 3-hydroxy-2-methylene-3-phenylpropionate methyl ester, was dissolved in acetic anhydride (113 ml; 1.20 mol), followed by addition of sulfuric acid (0.2 ml), and the resulting mixture was stirred at 100 °C for 4 hours. The reaction solution was concentrated under reduced pressure, to give a crude product of the title compound at a yield of 143.9 g. ^{1}H-NMR analysis revealed that the compound was a mixture of the E form and the Z form at a ratio of 87:13.

E form

^{1}H-NMR ($CDCl_3$) d: 2.09(3H, s), 3.82(3H, s), 4.95(2H, s), 7.35-7.45(5H, m), 7.98(1H, s).

Reference Example 3

Synthesis of 2-benzylidene-3-hydroxypropionic acid:

[0027] The product (143.9 g) in Reference Example 2, namely 2-benzylidene-3-acetoxypropionate methyl ester, was dissolved in methanol (400 ml), followed by addition of an aqueous solution of sodium hydroxide (96.0 g; 2.40 mol; purity of 97 %) in water (800 ml). The resulting mixture was stirred at ambient temperature for 90 minutes. The reaction solution was concentrated under reduced pressure to distill off methanol, followed by addition of water (100 ml) and 36 % hydrochloric acid (250 ml) for adjusting the resulting mixture to neutrality and subsequent extraction into ethyl acetate (600 ml). The resulting organic phase was washed with saturated saline (300 ml). After filtering off insoluble matters, the resulting solution was concentrated under reduced pressure. To the resulting residue was added toluene (250ml × 4), and the mixture was concentrated under reduced pressure to remove acetic acid to give a crude product of the title compound (107.8 g).

E form

^{1}H-NMR ($CDCl_3$) d: 4.53(2H, s), 7.40-7.55(5H, m), 7.97(1H, s).

MS (ESI)

177.0 ((M-H)-).

Reference Example 4

Synthesis of 2-hydroxymethyl-3-phenylpropionic acid:

[0028] The product (107.8 g) in Reference Example 3, namely 2-benzylidene-3-hydroxypropionic acid, was dissolved in methanol (500 ml), followed by addition of triethylamine (100 ml; 717 mmol) and 5 % palladium-carbon (5.00 g; water

content of 52.7 %) for catalytic reduction in hydrogen atmosphere for 50 hours. The reaction solution was filtered through Celite, to remove the palladium-carbon. The resulting filtrate was subjected to HPLC analysis, indicating that the filtrate contained the title compound (71.0 g; 394 mmol) (at a yield of 65.7 % (on a benzaldehyde basis)). The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in ethyl acetate (600 ml), followed by addition of water (600 ml) and 37 % hydrochloric acid (150 ml) and subsequent agitation, to extract the resulting organic phase. The organic phase was washed with an aqueous mixture solution of water (240 ml) and 37 % hydrochloric acid and then with saturated saline (300 ml), and dried over anhydrous sodium sulfate. By filtering off the resulting dried matter, the solution was concentrated under reduced pressure, to give a crude product of the title compound. The crude product was dissolved in ethyl acetate (150 ml), followed by addition of hexane (450 ml), and the resulting mixture was gradually cooled from 60 °C to 5 °C, to precipitate crystal, which was then filtered and dried to recover the title compound (48.45 g at a purity of 96.5 %; 295.5 mmol).
^{1}H-NMR ($CDCl_3$) d: 2.83-2.94(2H, m), 3.09 (1H, m), 3.70-3.83(2H, m), 7.20-7.33(5H, m).

Reference Example 5

Synthesis of (S)-2-hydroxymethyl-3-phenylpropionic acid:

[0029] To (RS)-2-hydroxymethyl-3-phenylpropionic acid (500.0 mg; 2.775 mmol) was added (1R, 2S)-(+)-cis-1-amino-2-indanol (311 mg; 2.085 mmol), followed by addition of 2-propanol (8 ml). While heating the mixture to 70 °C under stirring, the resulting mixture was dissolved therein, followed by gradual cooling. Finally, crystal was precipitated under cooling in an ice bath. The precipitated crystal was filtered under aspiration, washed with a small volume of 2-propanol, and dried under reduced pressure, to give the salt of(S)-2-hydroxymethyl-3-phenylpropionic acid · (1R,2S)-(+)-cis-1-amino-2-indanol (361.1 mg; 79.0 % as the yield on the salt basis; optical purity of 95.0 % ee). The resulting salt was recrystallized in 2-propanol, to give the salt of (S)-2-hydroxymethyl-3-phenylpropionic acid · (1R,2S)-(+)-cis-1-amino-2-indanol at 100 % ee (92 %). The double decomposition of the resulting salt with hydrochloric acid and extraction into ethyl acetate afforded (S)-2-hydroxymethyl-3-phenylpropionic acid (yield of 95 %).

Example 1

Synthesis of N-[(S)-2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester: ·

[0030] (S)-2-Hydroxymethyl-3-phenylpropionic acid (9.00 g; purity of 98.5 %; 49.22 mmol) and glycine benzyl ester · p-toluene sulfonic acid salt were suspended in tetrahydrofuran (90 ml), followed by addition oftriethylamine (7.55 ml; 54.17 mmol) and 2-hydroxybenzotriazole · monohydrate (7.32 g; 54.17 mmol), and the resulting mixture was cooled down to 3 °C. To the solution was dropwise added a solution of dicyclohexylcarbodiimide (11.17 g; 54.14 mol) in tetrahydrofuran (22 ml) over 15 minutes while the solution was kept at 3 to 4 °C, for subsequent reaction at 3 to 4 °C for one hour. After elevating the temperature to ambient temperature, the reaction further progressed for 15 hours. After the precipitated dicyclohexylurea was filtered off, the resulting solution was concentrated under reduced pressure. Then, the resulting residue was dissolved in toluene (100 ml) and ethyl acetate (150 ml), followed by addition of 1 mol/liter hydrochloric acid (200 ml). The resulting mixture was stirred for one hour. After the generated solid was filtered and washed with ethyl acetate (50 ml), the organic phase was separated. The resulting organic phase was sequentially washed with 1 mol/liter hydrochloric acid (60 mol), an aqueous saturated sodium hydrogen carbonate solution(sequentially in 150 ml and 50 ml) and saturate saline (100 ml) and then dried over anhydrous sodium sulfate. After the sodium sulfate was filter off, the organic phase was concentrated to give a crude product of the title compound. The HPLC analysis revealed that the organic phase contained the title compound at 15.86 g (48.44 mmol) (reaction yield of 98.4 %; optical purity > 99 % ee).
m.p.: 62 °C
^{1}H-NMR($CDCl_3$) d:2.65(H, ms),2.78(1H,dd),3.01(1H,dd), 3.70-3.80(2H,m),3.87(1H,dd),
4.17(1H,dd),5.14(1H,d),5.19(1H,d), 5.18(1H,br.t),7.18-7.41(10H,m).
MS (ESI)
328.3 (MH+)
[α]D -52.5° © 1.00, MeOH, 25 °C)

Example 2

Synthesis of N-[(S)-2-methanesulfonyloxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester:

[0031] The product in Example 1, namely N-[(S)-2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (15.86

g; 48.44 mmol) was dissolved in toluene (100 ml)and pyridine (15.7 ml; 194.1 mmol), followed by addition of methanesulfonyl chloride (9.37 ml; 121.1 mmol), and the resulting mixture was stirred at ambient temperature for 17 hours. To the reaction solution was added 1 mol/liter hydrochloric acid (150 ml), and the resulting mixture was stirred for 30 minutes. Then, the mixture was subjected to phase separation, and to the resulting organic phase was added an aqueous saturated sodium hydrogen carbonate solution (100 ml). The mixture was then stirred for 30 minutes, followed by phase separation. The resulting organic phase was further washed with saturated saline (100 ml), for HPLC analysis, which indicated that the organic phase contained the title compound at a yield of 19.33 g(47.87 mmol; reaction yield of 98.4 %). The organic phase was concentrated, and by subsequently adding toluene (250 ml)to the resulting residue, the residue was dissolved under heating. After filtering off insoluble matters, hexane (100 ml) was added to the resulting solution, followed by heating to 55 °C for dissolving the residue. By gradually cooling the resulting solution to 5 °C, the precipitated crystal was obtained by filtration and washed with toluene/hexane (=1/1; 60 ml in total), to give the title compound (17.99 g) (yield after crystal isolation = 91.6 %).

m.p.: 83 °C

^{1}H-NMR($CDCl_3$) d:2.75-2.98(3H,ms),3.98(3H,s),3.89(1H,dd), 4.10(1H,dd),4.28(1H,dd),4.39(1H,dd),5.15(2H,s),5.97 (1H,br .t.), 7.15-7.40(10H,m).

MS (ESI)

306.3 (MH+)

[α]D -33.3° © 1.04, MeOH, 25 °C)

Example 3

Synthesis of N-[(S)-2-bromomethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester.

[0032] The product in Example 2, namely N-[(S)-2-methanesulfonyloxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (16.95 g;42.0 mmol), was dissolved in acetone (120 ml), followed by addition of lithium bromide (7.30 mg; 84.0 mmol) for heating under reflux for 24 hours. After the completion of the reaction, the solvent was distilled off, and ethyl acetate (120 ml) and water (50 ml) were added. The organic layer was separated and then dried over anhydrous magnesium sulfate. After magnesium sulfate was filtered off, the resulting matter was concentrated, to give a crude product of the title compound. HPLC analysis revealed that the title compound was contained in the product at a yield of 16.07 g (41.17 mmol) (reaction yield of 98.0 %).

m.p.: 95 °C

^{1}H-NMR($CDCl_3$) d:2.80-3.02(3H,m),3.41(1H,dd),3.61(1H,dd), 3.95(1H,dd),4.10(1H,dd),5.16(2H,B),5.92(1H,br.t), 7.15-7.38(10H,m).

MS (ESI)

390 (MH+)

[α]D -33.8° © 1.00, MeOH, 25 °C)

Example 4

Synthesis of N-[(S)-2-acetylthiomethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester.

[0033] The product in Example 3, namely N-[(S)-2-bromomethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (834.5 mg;2.14 mmol), was dissolved in methyl isobutyl ether (4 ml), followed by addition of potassium thioacetate (256.8 mg; 2.57 mmol) and stirring at 50 °C for 3.5 hours. After the completion of the reaction, the organic phase was extracted into ethyl acetate (30 ml) and water (5 ml), and was then washed with an aqueous saturated sodium hydrogen carbonate solution (5 ml) and saturated saline (5 ml),followed by addition of active charcoal (2 mg) and stirring at ambient temperature for 20 minutes. The resulting matter was dried over anhydrous magnesium sulfate. After the active charcoal and magnesium sulfate were filtered off, the resulting matter was concentrated, to give a crude product of the title compound (842.3 mg). By adding methyl t-butyl ether (4.2 ml) to the resulting crude product and cooling the mixture from ambient temperature to 0 °C under stirring, crystal was precipitated. The precipitated crystal was filtered and washed with methyl t-butyl ether (1 ml), to give the title compound (416.4 mg; yield of 50 % after crystal isolation; optical purity > 99 % ee).

m.p.: 59-60 °C

^{1}H-NMR($CDCl_3$) d:2.31(3H,s), 2.62-2.67(3H,m), 2.62-2.67(3H,m), 2.87-3.07(2H,dd), 3.08-3.11(1H,dd), 3.85(1H,dd), 4.07(1H,dd), 5.13(2H,s), 5.83 (1H,br.t.), 7.14-7.39(10H,m).

MS (ESI)

386.2 (MH+)

[α]D +23.0° © 1.00, MeOH, 25 °C)

Example 5

Synthesis of N-[(S)-2-acetylthiomethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester.

[0034] Potassium thioacetate (386 mg; 3.31 mol) was suspended in methyl isobutyl ether (6 ml), followed by dropwise addition of a solution of N-[(S)-2-methanesulfonyloxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (812.9 mg; 2.01 mmol) in methyl isobutyl ether (11 ml), and the resulting mixture was stirred at ambient temperature for 3 hours. After the completion of the reaction, an aqueous saturated sodium hydrogen carbonate solution (20 ml) was added to the resulting matter, and then, the organic phase was extracted, washed with saturated saline (20 ml) and dried over magnesium sulfate. After filtering off magnesium sulfate, the resulting matter was concentrated. Subsequently, the resulting residue was purified by silica gel chromatography, to recover the title compound of 742.7 mg(at a yield of 97 %).

Example 6

Synthesis of N-[(S)-2-(p-toluenesulfonyl)methyl-1-oxo-3-phenylpropyl]-glycine benzyl ester.

[0035] 327.4 mg of N-[(S)-2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (1.0 mmol), was dissolved in dichloromethane (5 ml), followed by addition of pyridine (0.18 ml; 2.2 mmol) and p-toluenesulfonyl chloride (381.3 mg; 2.0 mmol) for stirring at ambient temperature for 4 days. The solvent was distilled off, and the resulting matter was subjected to silica gel chromatography with an ethyl acetate-hexane solution, to give the title compound at a yield of 373.1 mg (0.77 mmol) (yield of 77.5 %).
^{1}H-NMR($CDCl_3$) d:2.42(3H,s), 2.73-2.87(3H,m), 3.90-3.94(2H,m), 4.05-4.21(2H,m), 5.14(2H,s), 6.05(1H,br.t.), 7.15-7.74(14H,m).
MS (ESI)
481.5 (MH+)

Example 7

Synthesis of N-[(S)-2-(p-nitrobenzenesulfonyl)methyl-1-oxo-3-phenylpropyl]-glycine benzyl ester.

[0036] 327.4 mg of N-[(S)-2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (1.0 mmol), was dissolved in dichloromethane (5 ml), followed by addition of pyridine (0.24 ml; 3.0 mmol) and p-toluenesulfonyl chloride (738.8 mg; 3.0 mmol) for stirring at ambient temperature for 20 hours. The solvent was distilled off, and the resulting matter was purified by silica gel chromatography with an ethyl acetate-hexane solution, to give the title compound of 331.6 mg (0.65 mmol) (yield of 65.0 %).
^{1}H-NMR($CDCl_3$) d:2.73-2.88(3H,m),3.84(1H,dd),4.03-(1H,dd),4.20(1H,dd),4.31(1H,dd),5.15(2H,s), 5.92(1H, br.t.), 7.08-7.40 (10H,m), 8.02-8.06(10H,m), 8.31-8.35(10H,m).
MS (ESI)
513.1 (MH+)

Example 8

Synthesis of N-[(S)-2-acetylthiomethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester

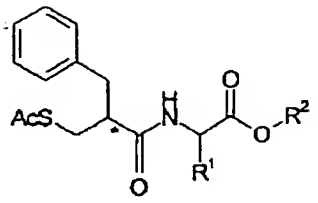
[0037] 157.3 mg of N-[(S)-2-(p-nitrobenzene sulfonyl)methyl-1-oxo-3-phenylpropyl]-glycine benzyl ester (0.31 mmol), was dissolved in methyl isobutyl ether (1 ml), followed by addition of potassium thiolacetate(70.0 mg; 0.61 mmol) for stirring at ambient temperature for 5 hours. After the completion of the reaction, ethyl acetate (20 ml) and an aqueous saturated sodium hydrogen carbonate solution (5 ml) were added to the reaction solution. The organic layer was separated, and was then dried over magnesium sulfate. After filtering off magnesium sulfate, the resulting matter was concentrated, to give the title compound (104.1 mg; 0.27 mmol; yield of 88.0 %).

[0038] As has been described above, in accordance with the present invention, optically active N-[(S)-2-acetylthiomethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester and related amino acid derivatives can be produced at low cost in an industrial manner.

Claims

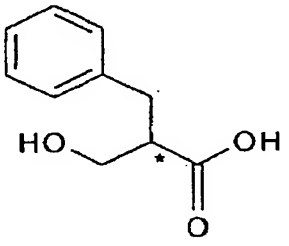
1. A method for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester represent-

ed by the general formula (IV);



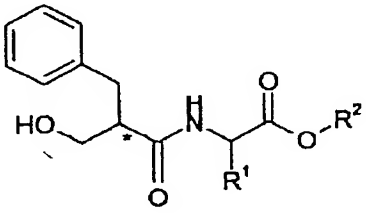
(IV)

(wherein R_1 represents hydrogen, an optionally substituted amino acid side chain or a protected amino acid side chain; R_2 represents an optionally substituted linear or branched C_1 to C_{18} alkyl group, or an optionally substituted benzyl group; and * denotes an optically active carbon atom),
comprising subjecting optically active 2-hydroxymethyl-3-phenylpropionic acid represented by the general formula (I);



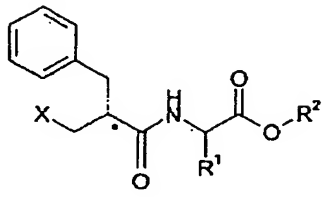
(I)

(wherein * denotes an optically active carbon atom) to reaction with an amino acid ester or a salt thereof to convert it into optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-amino acid ester represented by the general formula (II);



(II)

(wherein R_1 and R_2 independently represent the same groups as described above; and * denotes an optically active carbon atom).
activating the hydroxyl group of the hydroxymethyl group at the 2-position for conversion of the compound of formula (II) into optically active N-acylamino acid ester represented by the general formula (III);



(III)

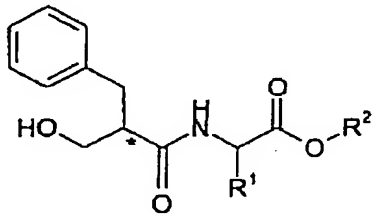
(wherein R_1 and R_2 independently represent the same groups as described above; X represents chloride, bromide, iodide, a linear, branched or cyclic C_1 - C_6 alkylsulfonyloxy group which may or may not have a substituent, or a C_6 - C_{18} arylsulfonyloxy group; and * denotes an optically active carbon atom),
and further subjecting the resulting optically active N-acylamino acid ester to reaction with a thioacetate salt or with thioacetic acid in the presence of a base.

2. A method according to claim 1, for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-glycine benzyl ester, wherein the amino acid ester or salt thereof is glycine benzyl ester or a salt thereof.

3. A method according to claim 1 or 2, wherein the optically active carbon atom is in the configuration S.

4. A method according to claim 1 or 2,wherein the optically active carbon atom is in the configuration R.

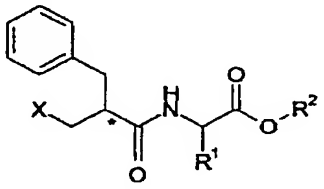
5. Optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-amino acid ester represented by the general formula (II) :



(II)

wherein R_1 and R_2 are as defined in claim 1 and * denotes an optically active carbon atom.

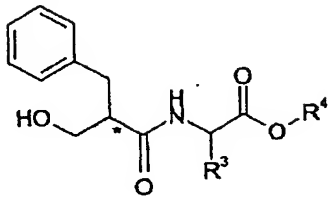
6. Optically active N-acylamino acid ester represented by the general formula III:



(III)

wherein R_1, R_2 and X are as defined in claim 1 and * denotes an optically active carbon atom.

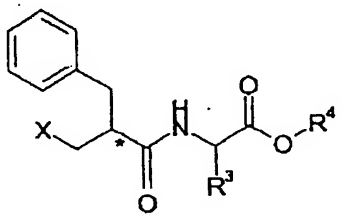
7. Optically active N-[2-hydroxymethyl-1-oxo-3-phenylpropyl]-glycine benzyl ester represented by the general formula (VI):



(VI)

(wherein R_3 represents hydrogen; R_4 represents a benzyl group; and * denotes an optically active carbon atom).

8. Optically active N-acyl-glycine benzyl ester represented by the formula (VII):



(VII)

(wherein X represents chloride, bromide, iodide, a linear, branched or cyclic C_1 - C_6 alkylsulfonyloxy group which may or may not have a substituent, or a C_6 - C_{18} arylsulfonyloxy group; R_3 represents hydrogen; R_4 represents benzyl group; and * represents optically active carbon atom).

9. An optically active compound according to any one of claims 5 to 8, wherein the optically active carbon atom is in the configuration S.

10. An optically active compound according to any one of claims 5 to 8,wherein the optically active carbon atom is in the configuration R.

11. A method according to any one of claims 1 to 4 wherein conversion of the compound of formula (I) into a compound of formula (III) is achieved by reaction of the compound of formula (I) with an amino acid ester or salt thereof in the presence of a halogenating agent capable of replacing hydroxyl groups by halogen atoms, and of converting carboxylic acid groups to acid halides.

12. A method for producing optically active N-[2-(acetylthiomethyl)-1-oxo-3-phenylpropyl]-amino acid ester of formula (IV) as set out in claim 1 comprising subjecting the optically active N-acylamino acid ester of formula (III) as set out in claim 1 to reaction with a thioacetate salt or with thioacetic acid in the presence of a base.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 1004

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	B.R. NEUSTADT, ET AL.: "Mercaptoacyl amino acid inhibitors of atrioprptidase. 1. Structure-activity relationship studies of methionine and S-alkylcysteine derivatives" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 15, 22 July 1994, pages 2461-2476, XP002019772 Washington, DC, US * scheme 3; table 1 *	1	C07C327/32 C07C231/02 C07C303/28
A	P. DEPREZ, ET AL.: "Thiol inhibitors of endothelin-converting enzyme" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 19, 8 October 1996, pages 2317-2322, XP004135830 Oxford, GB * scheme; compound 8 *	1	
A	FR 2 744 446 A (BIOPROJET) 8 August 1997 * examples 3,4 *	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	M. NAKANO, ET AL.: "Synthesis of renin inhibitors containing a sulphonylmethylene isostere at their N-terminals" CHEMISTRY LETTERS, no. 4, April 1990, pages 505-508, XP002104083 Tokyo, JP * compounds 7a,12a,13a,14a,14b *	1	C07C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 May 1999	English, R

CATEGORY OF CITED DOCUMENTS

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28-05-1999

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